REMARKS

Claims 34-48 have been added. Claims 21, 24, and 29-48 will be pending in the application after entry of this amendment. Applicants submit that the amendments do not present new matter and are fully supported by the specification. The amendments to the claims further streamline the language of the claims so that the claimed subject matter is more easily understood. Entry of the Amendment is respectfully requested. Applicants believe the claims are in condition for allowance.

Terminal Disclaimer

The Applicants file herewith an amended Terminal Disclaimer. Applicants believe this Terminal Disclaimer overcomes the Examiner's rejection based upon double patenting. The disclaimer is made to expedite issuance and is not intended as an admission that any claim of the invention is the same or an obvious variation of those of U.S. Patent No. 6,121,003.

Objections

In the Office Action mailed January 8, 2004, the Examiner objected to the form of Claim 30. Applicant believes that the amendments to the claims obviate this objection.

Rejections

35 U.S.C. sec. 112

The Examiner rejected claims 21, 24, and 29-33 based upon 35 U.S.C. sec. 112, second paragraph. Applicants respectfully traverse this rejection. The Applicants' have amended these claims. Applicants believe that the amendments to the claims put the claims in condition for allowance.

The Examiner also rejected claims 21, 24, 29-33 under 35 U.S.C. sec. 112, first paragraph. Applicants respectfully traverse this rejection. However, Applicants have amended the claims in a manner that Applicants believe places these claims in condition for allowance.

35 U.S.C. sec. 103

The Examiner rejected claims 21, 24, and 30 as being obvious in view of Dickson, Kosik, and Binder. Applicants respectfully traverse this rejection. The invention disclosed in this application has characteristics that are unique and undisclosed, and not known in the art. Page 4, starting at line 1 of the Specification supports this fact, noting that none of the antibodies described had absolute specificity in the art. "None of all the antibodies described heretofore has had an absolute specificity for the abnormally phosphorylated tau, either by immunohistology, Western blotting, or ELISA."

Claims 21, 24 and 30 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Dickson et al. in view of Kosik et al. and Binder et el. According to the Examiner, it would have been obvious to make additional monoclonal antibodies to the ones taught by Dickson making use of the method disclosed in Binder et al. and making use of the Tau 1 epitope as disclosed in Kosik et al.

Applicants note that the monoclonal antibodies of the claimed invention have specific binding characteristics that are recited in the claims. In particular, the claimed antibodies:

- bind a phosphorylated epitope present in human abnormally phosphorylated tau protein;
- do not bind non-phosphorylated tau protein;
- do not bind to the phosphorylated epitope after treatment with a dephosphorylating agent;
- do form an immunological complex with a peptide YSSPGSPGT or YSSPGSPGT.

* * *

None of the references cited by the Examiner disclose a monoclonal antibody having these characteristics, nor do they explain the process for the preparation of such a monoclonal

antibody. Further, there is no suggestion in the references cited by the Examiner to combine these references in order to arrive at the monoclonal antibodies of the claimed invention.

Dickson et al., as previously discussed, does not teach monoclonal antibodies with the characteristics of the monoclonal antibodies of the invention. The monoclonal antibodies of the claimed invention specifically bind abnormally phosphorylated tau protein, and do not recognize normally phosphorylated tau proteins which are present in brain homogenates derived from patients that died of a non-neurological disease. The antibody of Dickson et al. (NP14), however, does bind normal tau from human brain (page 255, left column, Results, line 6-7). Therefore, even if the skilled person could make "additional" antibodies similar to the ones taught by Dickson et al., those "additional" antibodies would not fulfill the characteristics of the antibodies of the claimed invention. Dickson et al. does not teach any antibody with the characteristics of the antibodies of the claimed invention, e.g., does not teach antibodies that bind abnormally phosphorylated tau proteins. Accordingly, Dickson et al. does not aid the skilled person in obtaining the antibodies of the claimed invention.

Kosik et al. and Binder et al. do not cure the deficiencies of the primary reference. These secondary references do not suggest or teach preparation of a monoclonal antibody with the characteristics of the monoclonal antibodies of the claimed invention, e.g., do not teach antibodies that specifically bind abnormally phosphorylated tau proteins. The preparation of a monoclonal antibody with the specific binding characteristics as indicated above, is a sequential process in which different steps (selections) have to be taken and without a reasonable expectation that an antibody with the desired binding characteristics will be obtained.

1. Selection of the immunogen

Different kinds of antigens are available for use in the immunization protocol and a selection needed to be made. The prior art documents cited by the examiner do not teach a specific immunogen that can be used in order to obtain a monoclonal antibody with the binding characteristics of the claimed monoclonal antibodies:

- Binder et al. teaches the use of bovine MAP and bovine tau as an immunogen for the preparation of monoclonal antibodies. Contrary to the examiner's assertion, we do not read that that Binder et al. uses Alzheimer basal forebrain. Binder et al. does not teach which antigen should be used in order to obtain the claimed monoclonal antibodies that specifically recognize abnormally phosphorylated tau and that do not recognize normally phosporylated tau proteins present in brain homogenates derived from the brain of a patient having died of nonneurological disease.
- In table 1 of Kosik et al. different monoclonal antibodies are shown as well as the immunogens used for their production: human and bovine MAPS, bovine tau, detergent extracts of rat brain protein and Alzheimer basal forebrain. However, none of the antibodies produced with these immunogens have the characteristics of the antibodies of the claimed invention. See, for example: "All of the antibodies (ten monoclonal and four polyclonal) react with all of the heat-stable tau isoforms prepared from bovine cerebrum by the taxol method or by temperature dependent articles of polymerization/depolymerization." (Kosik et.al., 1988, at page 817, last paragraph)

  Kosik et al. does not indicate which of these antigens should be selected in order to obtain a monoclonal antibody with the characteristics of the monoclonal antibodies of the invention. In fact, Kosik et al. would rather lead the skilled person away from the present invention. Kosik et al. shows that the use of an antigen (Alzheimer fatal basal forebrain), similar to the antigen used in the present invention (tau protein isolated from AD brain) as an immunogen leads to the isolation of a monoclonal antibody (Alz50) with characteristics different from the characteristics of the claimed monoclonal. Accordingly, Kosik et al. would rather teach the skilled person away from using Alzheimer basal forebrain.

2. Screening for the monoclonal antibody with the desired characteristics

Different kinds of screening procedures are available for use in the selection of the hybridoma that secretes a monoclonal antibody with the desired characteristics. The present inventors selected a sandwich ELISA with polyclonal rabbit anti-human tau antibodies affinity purified with affinity purified human tau. The references cited by the Examiner do not disclose

this screening assay or a screening assay similar to this. The references do not teach that such a screening assay can be used to isolate a hybridoma producing a monoclonal antibody with the characteristics of the monoclonal antibodies of the invention.

- As indicated by the Examiner, Binder et al. teaches the use of a competitive ELISA to measure the level of tau or microtubulin. Binder el al. does not teach that this competitive ELISA can be used to select a monoclonal antibody with the characteristics of the monoclonal antibodies of the invention. Binder el al. do not teach which adaptation is needed in order to use this competitive ELISA in a screening assay to obtain a monoclonal antibody with the characteristics of the monoclonal antibodies of the invention. Nowhere Binder et al. do not teach the sandwich ELISA used in the method of the present invention or how to select between monoclonal antibodies in order to obtain the desired antibody. Binder et al. do not teach how to select a monoclonal antibody with the characteristics of the monoclonal antibodies of the present invention.

- Kosik et al. teach the epitope that is recognized by Tau-1 and which is phosphatase sensitive. According to the Examiner, "one would have been motivated to screen for those monoclonal antibodies which recognize the phosphorylated epitope to which the Tau-1 for detection and diagnosis of brain." Kosik et al., however, do not teach how this epitope should be used in a screening assay in order to obtain the monoclonal antibodies of the invention. In fact, the use of this epitope as such in a screening assay for monoclonal antibodies would not result in the selection of a monoclonal antibody with the characteristics of the monoclonal antibodies of the present invention.

  Kosik et al. do not teach how to obtain a phosphorylated epitope that could be used in the selection of a monoclonal antibody with the desired characteristics. One skilled in the art does not have any guidance where phosphorylation should occur in order to obtain any epitope recognized by the monoclonal antibodies of the present invention. In fact, Kosik et al. teaches away from obtaining a phosphorylated epitope with the epitope sequence of Tau-1 (page 820, left column, lines 48-53).

Finally, the use of a peptide instead of a full protein could result in a different conformation of the epitope to be recognized. Accordingly, antibodies that would normally not be recognized might be missed. Therefore, by using the peptide as disclosed in Kosik et al. for screening, there was no reasonable expectation of success that the monoclonal antibodies of the present invention could be obtained.

The Examiner also rejected claims 29 and 31-33 as being obvious in view of Dickson, Kosik and Binder and in further view of Trojanowski and Catty. Applicants respectfully traverse this rejection. None of the references teach or suggest the monoclonal antibodies with the characteristics of the present invention, as discussed above. Similarly, Trojanowski and Catty do not disclose the present invention, nor does it teach the monoclonal antibody for the uses described in the present invention.

In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

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